PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
X62816PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/006265	09.06.2004	10.06.2003

International Patent Classification (IPC) or national classification and IPC
C07K14/47, A61K38/17

Applicant
XANTOS BIOMEDICINE AG et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.04.2005	20.10.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006265

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-65	as originally filed
Sequence listings part of the description, Pages	
1-36	as originally filed
Claims, Numbers	
1-20	received on 11.04.2005 with letter of 11.04.2005
Drawings, Sheets	
1/23-23/23	as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 18,19 (I.A.)

because:

☒ the said international application, or the said claims Nos. 18,19 (I.A.) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10,17
	No:	Claims	1-9,11-16,18-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-17,20
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.

PCT/EP2004/006265

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 18-19 relate to methods potentially comprising testing steps in human subjects. Therefore this subject-matter is considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 02/053737 A (NAGANO YUKIKO ; HONDA GOICHI (JP); MATSUDA AKIO (JP); MURAMATSU SHUJI) 11 July 2002 (2002-07-11)

D2: WO 99/06552 A (GENSET SA ; LACROIX BRUNO (FR); DUCLERT AYMERIC (FR); DUMAS MILNE EDWA) 11 February 1999 (1999-02-11)

D3: DATABASE EMBL EBI; 4 January 2002 (2002-01-04), STRAUSBERG RL ET AL.: "Mus musculus RIKEN cDNA D430028G21 gene, mRNA (cDNA clone MGC:25836 IMAGE:4190175), complete CDS." XP002297872 Database accession no. BC020006

D4: DATABASE EMBL EBI; 30 January 2003 (2003-01-30), STRAUSBERG RL ET AL.: "Homo sapiens KIAA1271 protein, mRNA (cDNA clone MGC:50830 IMAGE:5751684), complete CDS." XP002297873 Database accession no. BC0044952

D5: MATSUDA AKIO ET AL: "Large-scale identification and characterization of human genes that activate NF-kappaB and MAPK signaling pathways." ONCOGENE. 22 MAY 2003, vol. 22, no. 21, 22 May 2003 (2003-05-22), pages 3307-3318, XP002297871 ISSN: 0950-9232

D6: THOMPSON J D: "Applications of antisense and siRNAs during preclinical drug development" DRUG DISCOVERY TODAY, ELSEVIER SCIENCE LTD, GB, vol. 7, no. 17, 1 September 2002 (2002-09-01), pages 912-917, XP002236964 ISSN:

1359-6446

D7: WO 03/048202 A (MATSUDA AKIO ; MURAMATSU SHUJI (JP); ASAHI CHEMICAL IND (JP)) 12 June 2003 (2003-06-12)

The present application relates to a human gene and protein, as well as a human isoform and a mouse orthologue, that promotes angiogenic (growth of new capillaries from existing ones) activity in certain cell types. Induces the production of VEGF and expression of other pro-angiogenic factors in HEK293 cells such as IL-8 and RANTES. Several inhibitors of the proteins are shown A.O. inhibitory antibodies (polyclonal and monoclonal, as well as fragments) and a short peptide derived from the extracellular domain. The claims relate to inhibitors to the above genes and proteins.

D1 discloses the cloning of human genes and the encoded proteins that activate NFkB function. SEQ ID NO: 170 has 51% identity with SEQ ID 2, 99.4% identity with SEQ ID 4 and 100% identity with SEQ ID 6 e.g. of a protein falling under the scope of claims 1-5. Use in cancer and ischemic disorders therapy is disclosed. Also disclosed are diagnostic materials (antibodies) for detecting A.O. cancers. Moreover are disclosed peptide and antibody inhibitors, as well as small molecule inhibitors, inhibitory antisense nucleotides, ribozymes and triplex forming nucleotides and antagonists of the genes and proteins in question. Since sSEP or SEP or derivatives thereof (see infra for clarity) can be considered derived from or being identical to either SEQ ID 170 or an almost identical sequence or a soluble derivative of SEQ ID 170, generic inhibitors to sSEP or SEP (plus derivatives) are standing against (the same) generic inhibitors to SEQ ID NO 170 (falling under the scope claims 1-5), thus creating a novelty problem.

D2 discloses the cloning and sequencing of 5' EST's of secreted proteins. SEQ ID NO: 153 has 100% identity in 61 amino acids with sequences SEQ ID 4 and 6 and shows clearly the secretion signal as well as 25 amino acids of the secreted form. This demonstrates that the proteins of SEQ ID 4 and 6 were known to be secreted proteins and that a gene and protein of D2 is falling under the scope of claims 1-5. Indeed in D2 it is considered that two peptides are revealed, one with the secretion signal and the mature one without that sequence, the secretion sequence being identified in the sequence listing with negative numbers and the mature portion (without a transmembrane domain) with positive numbers, starting from +1.

This is readily disclosed to a skilled artisan when considering D2. Also disclosed are various uses of the proteins in diseases like cancer, rheumatoid arthritis etc as well as antibody inhibitors, inhibitory antisense nucleotides and triplex forming nucleotides.

Hence D1 and D2 anticipate novelty of claims 1-7 and also 9, 11-16, 18-20.

Claim 8, with respect to SEQ ID NO's 26 and 27 can be considered novel. However this is only an optional feature and the claim relates to a fragment of "SEP" (whatever this means, see also below) inhibiting "sSEP". There is no structural limitation with respect to length and sequence of the peptides disclosed and so this information is considered in nothing more relevant than say a generic peptide or protein of D1 inhibiting function of SEQ ID 170 of D1. For the moment therefore claim 8 is not considered novel over D1.

In conclusion, D1 and D2 anticipate novelty of claims 1-9, 11-16, 18-20 which are thus not in accordance with Article 33(2) PCT and also not based on inventive step contrary to the requirements of Article 33(3) PCT.

At present is also not apparent in how far claims 10 and 17 e.g use of an inhibitor of "SEP" in conjunction with an inhibitor of VEGF, which is to be considered novel under Article 33(2) PCT in view of the prior art documents on file, would be based on inventive step as no such inhibitor mix is shown to be of any use or to have any effect. Hence, claims 10 and 17 are not considered to be based in inventive step contrary to Article 33(3) PCT.

Also the inhibitor in connection with full-length SEQ ID 4 and SEQ ID 6 is not considered inventive since D3-D5 disclose to 100% these sequences and a simple combination with e.g. D1 and D2 would have shown the relatedness of theses sequences and the possibility to apply the inhibitors of D1 and D2 to these sequences. Furthermore the siRNA embodiment in claim 6 not considered build on inventive step since D6 shows the usefulness to the skilled person for using antisense oligonucleotides and siRNA in knocking-out gene function. So even if this is not specifically mentioned in D1 and D2 it something obvious to propose for an alternative inhibitor for a skilled person wishing to knock out gene function of a gene, of the sequences indicated above, of D1 and D2.

Re Item VI

Certain documents cited

D7 cited P,X in the search report discloses the cloning of human and mouse genes and the encoded proteins that activate NFkB function. SEQ ID NO: 44 (mouse) has 100% identity with SEQ ID 2, 51% identity with SEQ ID 4 and 51% identity with SEQ ID 6. SEQ ID NO: 46 (human) has 51% identity with SEQ ID 2, 99.4% identity with SEQ ID 4 and 100% identity with SEQ ID 6. Use in cancer and ischemic disorders therapy is disclosed. Also disclosed are diagnostic materials (antibodies, DNA's and others) for detecting A.O. cancers. Moreover are disclosed peptide and antibody inhibitors, as well as small molecule inhibitors, inhibitory antisense nucleotides, ribozymes and triplex forming nucleotides and antagonists. D7 is relevant for novelty of claims 1-9, 11-16, 18-20.

Re Item VIII

Certain observations on the international application

Article 6 PCT (clarity issues).

Throughout the claims the term "inhibitor of sSEP" is used without giving any structural indication to what such an inhibitor would be. This clearly describes a desideratum but not a solution to a technical problem.

The term "soluble" in the claims is not clear. Indeed if it is not said in which medium a compound should be soluble then this notion is not of much help. For example membrane bound proteins are not soluble in a buffer without detergents but can well be solubilised in buffers comprising such detergents or other chaotropic agents. Thus such membrane proteins are also soluble, depending on the solvent employed.

The terms SEP and sSEP used in the claims are private protein designations that have no recognised meaning in the art. Hence they are prone to subjective interpretation and utmost unclear. Also the fact that these terms are explained in the description is of no help for assessing novelty and clarity, because in accordance with Article 6, Rule 6 PCT, claims must be self-contained.

The terms "functional active soluble derivative" or "functional active variant" used throughout the claims is totally unclear since it is not apparent for the claims what structure and or function is to be imposed on such a derivative in order for it to be encompassed or not within the claim.

Claims 6 and 8 relate to "fragments of SEP" that neither defined by sequence nor by a minimal length of one of the proteins of the application. It cannot be appreciated what falls under the scope of such a claim.

The term "homology of at least 25%" in claim 2 is unclear. There are dozens of different models for appreciating protein homology, nonetheless it is not specified in the claims which method is used for appreciating the homology.

Claims

1. An inhibitor of the sSEP or a functional active soluble derivative thereof or of the SEP as defined in SEQ ID NO: 2 or 4 or of a functional active derivative thereof.

2. The inhibitor of claim 1, wherein the derivative of sSEP exhibits a sequence homology of at least 25 % to the sSEP.

3. The inhibitor of any of claims 1 or 2, wherein the sSEP or functional derivative thereof is devoid of a transmembrane domain of SEP or of a functional active variant thereof.

4. The inhibitor of any of claims 1 to 3, wherein the sSEP or functional derivative thereof has a C-terminal amino acid corresponding to amino acid 510, 249, 246, 242, 171 or 167 of SEP according to SEQ ID NO: 4 or has a C-terminal amino acid corresponding to the equivalent amino acid of a sSEP derivative.

5. The inhibitor of any of claims 1 to 3, wherein the sSEP or functional derivative thereof has the sequence as shown in any of SEQ ID NO: 7 to 18.

6. The inhibitor of any of claims 1 to 5, selected from the group consisting of antibodies, peptides, fragments of SEP, antisense oligonucleotides, siRNA, Low molecular weight molecules (LMWs) and SEP receptor antagonists.

7. The inhibitor of claim 6, wherein the inhibitor is an antibody, preferably a polyclonal or monoclonal antibody or fragment thereof.

8. The inhibitor of claim 6, wherein the inhibitor is a fragment of SEP, preferably a peptide having the sequence as shown in SEQ ID NO: 26 or 27.

9. A pharmaceutical composition, comprising the inhibitor of any of claims 1 to 8, optionally in combination with a pharmaceutically acceptable carrier.

10. The pharmaceutical composition of claim 9, further comprising a VEGF inhibitor.

11. The inhibitor of any of claims 1 to 8, for use in therapy.

12. Use of an inhibitor of the sSEP or a functional active soluble derivative thereof or of the SEP as defined in SEQ ID NO: 2, 4 or 6 or of a functional active derivative thereof for the preparation of a pharmaceutical composition for the treatment of a disease selected from the group consisting of cancer, rheumatoid arthritis, psoriasis, artherosclerosis, retinopathy, osteoarthritis, endometriosis and chronic inflammation.

13. The use of claim 12, wherein the inhibitor is defined as in claims 2 to 8.

14. The use of claim 12 or 13, wherein the inhibitor prevents the formation of vascular vessels in the tumor tissue.

15. The use of any of claims 12 to 14, wherein the inhibitor inhibits the production of VEGF, IL-8 and/or RANTES.

16. The use of any of claims 12 to 15, wherein the cancer is selected from the group consisting of brain cancer, pancreas carcinoma, stomach cancer, colon carcinoma, skin cancer, especially melanoma, bone cancer, kidney car-

cinoma, liver cancer, lung carcinoma, ovary cancer, mamma carcinoma, uterus carcinoma, prostate cancer and testis carcinoma.

17. The use of any of claims 12 to 16, in combination with a VEGF inhibitor.

18. A method for the identification of a SEP inhibitor, wherein a potential inhibitor is tested for its activity to block the effects of SEP as defined in SEQ ID NO: 2 or 4 or of a functional derivative thereof.

19. A method for the preparation of a pharmaceutical composition, wherein a SEP inhibitor is identified according to claim 18, synthesized in adequate amounts and finally formulated into a pharmaceutical composition.

20. Use of SEP as defined in SEQ ID NO: 2 or 4, sSEP or a derivative thereof for the identification of proteins that bind or interact with SEP, wherein

a) a potential SEP interactor is brought into contact with SEP or a functional derivative thereof, and

b) binding of the potential interactor to SEP or the functional derivative thereof is determined.